Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Cyclosporin A, currently marketed as Neoral® and Sandimmune® (Novartis), is the most widely prescribed drug for the prevention of organ transplant rejection. Cyclosporin A has also demonstrated clinical efficacy in the treatment of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, psoriasis, and Type I diabetes and chronic inflammatory diseases like asthma. Test results in many other preclinical studies indicate utility for cyclosporin A in other therapeutic areas.

Widespread use of cyclosporin A for clinical uses other than prevention of organ transplant rejection is limited, however, due to the drugs narrow therapeutic index. Long term toxicity from chronic administration of cyclosporin A is a serious drawback. Negative consequences associated with chronic treatment with cyclosporin A include nephrotoxicity, abnormal liver function, hirsutism, tremor, neurotoxicity, gastrointestinal discomfort, and other adverse effects. Toxicity associated with cyclosporin A usage has been attributed by many experts working in the immunosuppression therapeutic area as mechanism based. Cyclosporin A inhibits the ubiquitous serine/threonine phosphatase called calcineurin. Attempts to separate the immunosuppressive activity from toxicity through structural modification of cyclosporin A have, for the most part, been unsuccessful. Nevertheless, over the past decade, continued investigation into understanding cyclosporin's toxicity has provided other possible explanations that are independent of calcineurin inhibition.

Published results of recent research suggest that cyclosporin A-mediated generation of reactive oxygen intermediates may be linked with the significant side effects that accompany use of this drug. Results of *in vitro* and *in vivo* studies indicate that although cyclosporin A is capable of generating reactive oxygen intermediates, the radicals formed are not derived directly from the cyclosporin A molecule, and are unlikely to stem from mitochondria or from cytochrome P450-mediated metabolism of cyclosporin A.

Novel cyclosporin A analogue, $ISA_{TX}247$, is a potent calcineurin inhibitor and has demonstrated a reduced toxicity profile relative to cyclosporin A in animal studies. It remains to be shown if this translates into reduced toxicity in human. Cyclosporin analogues have been disclosed, where the $MeBmt^1$ ((4R)-4-((E)-2-butenyl)-4,N-dimethyl-L-threonine)

amino acid side chain of cyclosporin A has been structurally modified. Some of the most active compounds have deuterium incorporated in place of one or more hydrogens in the side chain. Incorporation of deuterium is known to slow down metabolism of compounds *in vivo*, if hydrogen abstraction is the rate limiting step in the metabolism of the drug and improve the pharmacokinetic properties of the molecule. Deuterium incorporation in cyclosporin A analogues may also block pathways responsible for generation of reactive oxygen intermediates in a manner not currently understood.

Other studies have implicated the role of transforming growth factor-β (TGF-β) in the nephrotoxicity of cyclosporin A. Cyclosporin A induces expression of TGF-β, collagen and fibronectin genes in the kidney. TGF-β has a host of immunosuppressive effects that parallel the effects of cyclosporin A. However, TGF-β also causes the accumulation of extracellular matrix genes by increasing the expression of collagen and fibronectin, which is the hallmark of fibrosis. Because glomerulosclerosis (which occurs with chronic cyclosporin A use) is associated with an increase of extracellular matrix proteins, cyclosporin A-associated nephrotoxicity may be due to TGF-β induction. Novel analogues of cyclosporin A may have different effects on induction of gene expression of proteins like TGF-β and may demonstrate improved therapeutic index.

Therefore, it would be advantageous to have novel cyclosporin derivatives that are safe and effective for the treatment of a variety of diseases.

The present invention is directed to achieving these objectives.

The rejection of claim 1 under 35 U.S.C. § 102(b) as anticipated by Wenger, "Structures of Cyclosporine and Its Metabolites," *Transplantation Proceedings* 22(3):1104-1108 (1990) ("Wenger") or by U.S. Patent No. 4,384,996 to Bollinger et al. ("Bollinger") is respectfully traversed in view of the above amendments and the following remarks.

Wenger describes some aspects of the conformation of the cyclosporin A molecule both *in vacuo* and in water and discloses structures of cyclosporin and its metabolites, as well as the synthesis of some known metabolites. However, as to the pending claims, Wenger fails to teach the limitation "with the proviso that...(4) when R_1 = $CR_{13}R_{14}R_{15}$, wherein $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, R_{15}, R_{14}, or R_{13}, respectively, cannot be...substituted or unsubstituted C_2-C_6-straight alkenyl...chain...." In the outstanding office action, it is asserted that Wenger, in Figure 1 on page 1104, teaches the compound of Formula (I) wherein A is an amino acid of Formula (II) and wherein R_0 is CH_3;

R_1 is $CR_{13}R_{14}R_{15}$, with $R_{13} = R_{14} = H$ and R_{15} = substituted or unsubstituted C_2-C_6-straight alkenyl chain, as claimed in the present application. However, by the above amendments, Formula (I) no longer permits substituent R_{15} to be a substituted or unsubstituted C_2-C_6-straight alkenyl chain. Since Wenger fails to teach or suggest compounds satisfying this limitation, it cannot anticipate the claimed invention.

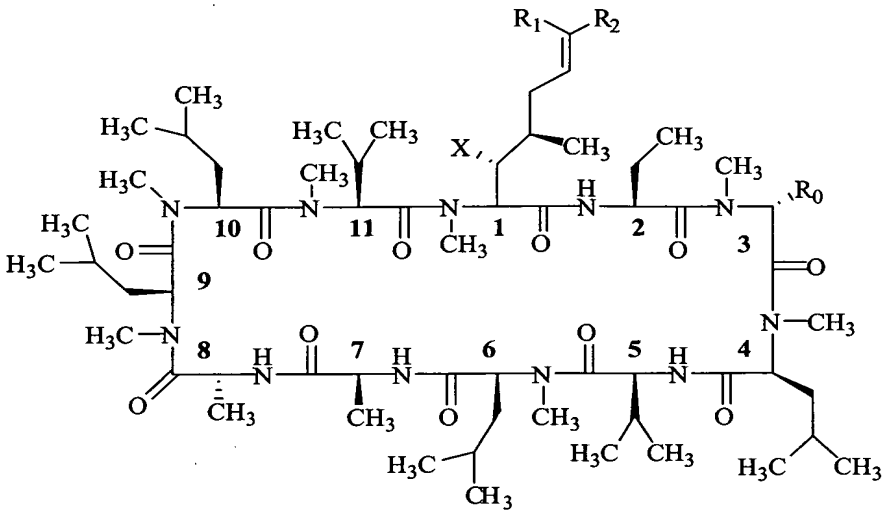
In addition, Bollinger discloses cyclosporins having a β-vinylene-α-amino acid residue at the 2-position and/or a β-hydroxy-α-amino acid residue at the 8-position, which are useful as immunosuppressive and anti-inflammatory agents, and processes for their production. However, as to the pending claims, Bollinger fails to teach the limitation "wherein...B is an amino acid selected from the group consisting of: α–aminobutyric acid; alanine; threonine; valine; norvaline; and a modified α–aminobutyric acid, alanine, valine, or norvaline, wherein a carbon atom in a side chain is substituted with a hydroxyl group" or the limitation "wherein...H is D-alanine...." In the outstanding office action, it is asserted that Bollinger, in columns 3 and 4, teaches the compound of Formula (I) wherein A is an amino acid of Formula (II) and wherein B is α–aminobutyric acid and H is D-alanine. However, while Bollinger does disclose cyclosporin compounds where Z_1 at the 2-position is ethyl (i.e., where B is α–aminobutyric acid in claim 1 of the present application), Bollinger, when the amino acid residue at the 2-position is not a β-vinylene-α-amino acid residue, requires the amino acid residue at the 8-position to be a β-hydroxy-α-amino acid residue, such as -(D)-Ser and -(D)-Thr (see column 2, lines 51-54 and 64-65), whereas claim 1 of the present application requires substituent H (at the 8-position) to be -(D)-alanine. Since Bollinger fails to teach or suggest compounds satisfying the limitations of the present claims, it cannot anticipate the claimed invention.

Accordingly, the rejection under 35 U.S.C. § 102(b) as anticipated by Wenger or by Bollinger should be withdrawn.

The objections to the specification for typographical errors and minor informalities are obviated in view of the above amendments to the specification.

The provisional rejection of claim 1 under the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-11 of copending U.S. Patent Application Serial No. 11/232,292 to Molino et al. ("Molino I") is respectfully traversed in view of the above amendments to claim 1 and the following remarks.

The compound claims of Molino I are drawn to: (1) a compound of Formula Ia:



Formula Ia

wherein:

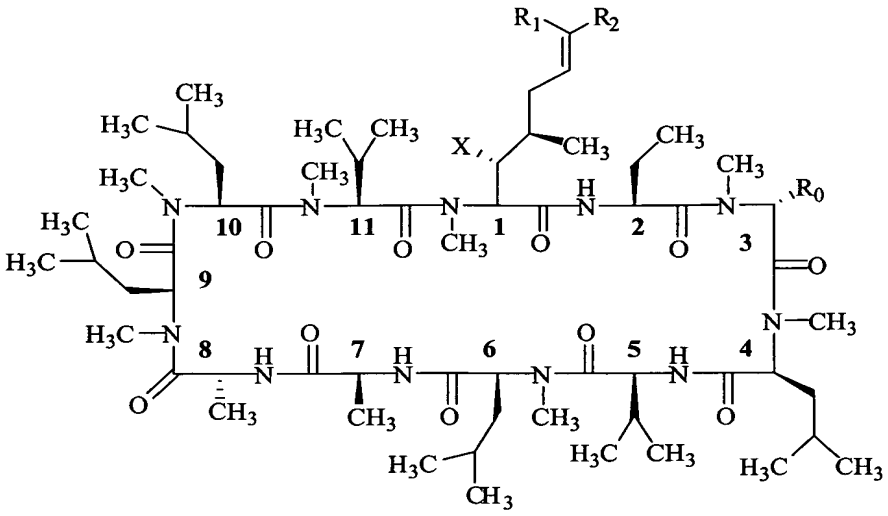
X is OH or OAc;

R_0 is H or CH_2OR_3;

R_1 is H or D;

R_2 is selected from the group consisting of:
halogen,
C_1-C_6 halogenated saturated straight or branched carbon chain,
C_2-C_6 halogenated unsaturated straight or branched carbon chain,
C_3-C_6 substituted and unsubstituted cycloalkyl,
C_1-C_6 saturated straight or branched carbon chain containing amino group,
-CH=N-OR_4, and
-CH=N-NR_4R_5;

...or a pharmaceutically acceptable salt thereof (claim 1) and (2) a compound of Formula Ib:



Formula Ib

wherein:

X is OH or OAc;

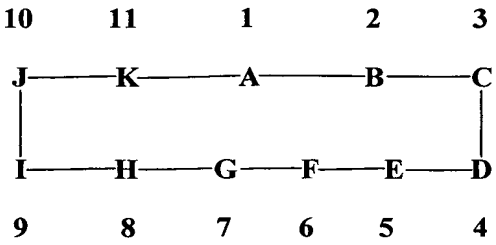
R_0 is H or CH_2OR_3;

R_1 is halogen;

R_2 is selected from the group consisting of:
hydrogen,
deuterium,
halogen,
C_1-C_6 saturated straight or branched carbon chain, optionally containing halogen,
C_2-C_6 unsaturated straight or branched carbon chain, optionally containing halogen,
C_3-C_6 substituted and unsubstituted cycloalkyl,
substituted and unsubstituted aryl, and
substituted and unsubstituted heteroaryl;

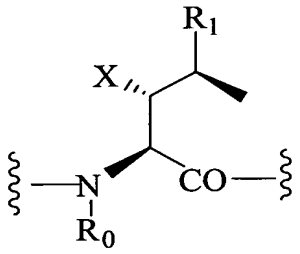
...or a pharmaceutically acceptable salt thereof (claim 9).

Thus, the compound claims of Molino I are not directed to "[a] compound of of Formula (I):



Formula I

wherein A is an amino acid of Formula (II):



Formula II

wherein:

R_0 is H or CH_3;

R_1 = CHO;
$C(=O)OR_2$;
$C(O)NR_3R_4$;
CH=N-Y;
$CH(NR_5R_6)R_7$;
$CH(OR_8)R_9$;
$CH(OR_{10})_2$;
$CH(SR_{12})_2$;
$CR_{13}R_{14}R_{15}$;
CH=CHC(=O)Me;
$CH_2CH_2C(=O)Me$;
$CH=CHCH(OR_{16})Me$;
$CH_2CH_2CH(OR_{16})Me$;
$CH=CHCH(NR_{17}R_{18})Me$;
$CH_2CH_2CH(NR_{17}R_{18})Me$;
CH=CHC(=N-Y)Me;
$CH_2CH_2C(=N-Y)Me$;
$CH=CHC(OR_{19})_2Me$;
$CH_2CH_2C(OR_{19})_2Me$;
$CH_2\text{-}CH_2C(=CR_{20}R_{21})Me$;
$CH=CHC(SR_{22})_2Me$;
$CH_2CH_2C(SR_{22})_2Me$;

$CH=CR_{23}R_{24}$;
$CH_2CHR_{23}R_{24}$;
$CH=CHC(=O)NR_{25}R_{26}$;
$CH_2CH_2C(=O)NR_{25}R_{26}$;
$CH=CHC(=O)OR_{26}$;
$CH_2CH_2C(=O)OR_{26}$;
$CH=CHC(=O)CH_2CH_2NR_{27}R_{28}$;
$CH_2CH_2C(=O)CH_2CH_2NR_{27}R_{28}$;
$CH=CHC(=O)CH=CHNR_{29}R_{30}$;
$CH_2CH_2C(=O)CH=CHNR_{29}R_{30}$;
$CH=CH\text{-}C(OR_{31})R_{32}Me$;
$CH_2CH_2C(OR_{31})R_{32}Me$;
$CH=CHC(=O)CH_2C(OH)R_{33}R_{34}$; or
$CH_2CH_2C(=O)CH_2C(OH)R_{33}R_{34}$; ...

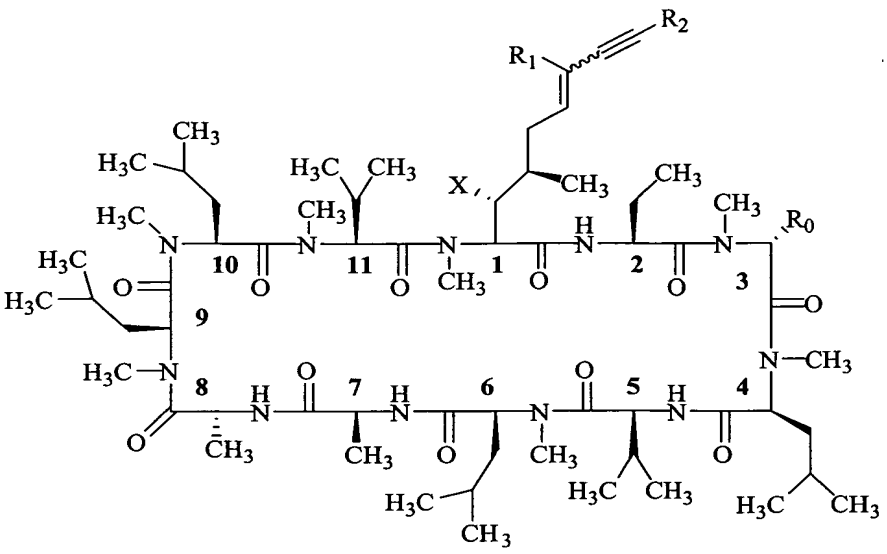
X = hydrogen;
hydroxyl; or
hydroxyl group derivatized with an alkanoyl, aryloyl, alkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, or arylalkyloxycarbonyl group;

...with the proviso that...(4) when $R_1 = CR_{13}R_{14}R_{15}$, wherein $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, R_{15}, R_{14}, or R_{13}, respectively, cannot be...substituted or unsubstituted C_2-C_6-straight alkenyl...chain (emphasis added)" as set forth in claim 1 of the present application.

Since the above amendments to claim 1 exclude the possibility of R_{15}, R_{14}, or R_{13} being a substituted C_2-C_6-straight alkenyl chain, when $R_1 = CR_{13}R_{14}R_{15}$, where $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, the provisional rejection of claim 1 under the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-11 of Molino I is improper and should be withdrawn.

The provisional rejection of claim 1 under the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending U.S. Patent Application Serial No. 11/232,360 to Molino et al. ("Molino II") is respectfully traversed in view of the above amendments to claim 1 and the following remarks.

The compound claims of Molino II are drawn to a compound of Formula I:



Formula I

wherein:

X is OH or OAc;

R_0 is H, CH_2OH, or CH_2OR_3;

R_1 is hydrogen, deuterium, or methyl;

R_2 is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 saturated or unsaturated, straight or branched carbon chain;

C_1-C_6 saturated or unsaturated, straight or branched carbon chain containing a substitution or substitutions selected from the group consisting of deuterium, halogen, nitrogen, sulfur, and silicon;

C_1-C_6 saturated or unsaturated, straight or branched carbon chain containing a function group or function groups selected from the group consisting of alcohol, ether, aldehyde, ketone, carboxylic acid, ester, and amide;

C_1-C_6 saturated or unsaturated, straight or branched carbon chain containing a function group of oxime or hydrazone;

C_1-C_6 saturated or unsaturated, straight or branched carbon chain containing an aryl or a heteroaryl group;

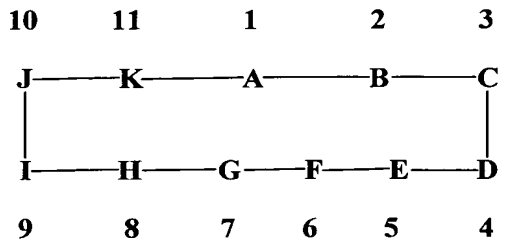
C_3-C_6 substituted and unsubstituted cycloalkyl;

substituted and unsubstituted aryl; and

substituted and unsubstituted heteroaryl;

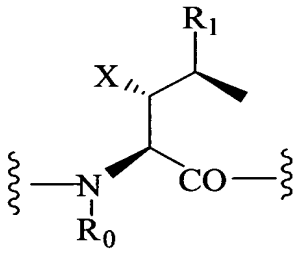
...or a pharmaceutically acceptable salt thereof (claim 1).

Thus, the compound claims of Molino II are not directed to "[a] compound of of Formula (I):



Formula I

wherein A is an amino acid of Formula (II):



Formula II

wherein:

R_0 is H or CH_3;

R_1 = CHO;
$C(=O)OR_2$;
$C(O)NR_3R_4$;
CH=N-Y;
$CH(NR_5R_6)R_7$;
$CH(OR_8)R_9$;
$CH(OR_{10})_2$;
$CH(SR_{12})_2$;
$CR_{13}R_{14}R_{15}$;
CH=CHC(=O)Me;
$CH_2CH_2C(=O)Me$;
$CH=CHCH(OR_{16})Me$;
$CH_2CH_2CH(OR_{16})Me$;
$CH=CHCH(NR_{17}R_{18})Me$;
$CH_2CH_2CH(NR_{17}R_{18})Me$;
CH=CHC(=N-Y)Me;
$CH_2CH_2C(=N-Y)Me$;
$CH=CHC(OR_{19})_2Me$;
$CH_2CH_2C(OR_{19})_2Me$;

CH_2-$CH_2C(=CR_{20}R_{21})Me$;
$CH=CHC(SR_{22})_2Me$;
$CH_2CH_2C(SR_{22})_2Me$;
$CH=CR_{23}R_{24}$;
$CH_2CHR_{23}R_{24}$;
$CH=CHC(=O)NR_{25}R_{26}$;
$CH_2CH_2C(=O)NR_{25}R_{26}$;
$CH=CHC(=O)OR_{26}$;
$CH_2CH_2C(=O)OR_{26}$;
$CH=CHC(=O)CH_2CH_2NR_{27}R_{28}$;
$CH_2CH_2C(=O)CH_2CH_2NR_{27}R_{28}$;
$CH=CHC(=O)CH=CHNR_{29}R_{30}$;
$CH_2CH_2C(=O)CH=CHNR_{29}R_{30}$;
$CH=CH$-$C(OR_{31})R_{32}Me$;
$CH_2CH_2C(OR_{31})R_{32}Me$;
$CH=CHC(=O)CH_2C(OH)R_{33}R_{34}$; or
$CH_2CH_2C(=O)CH_2C(OH)R_{33}R_{34}$; ...

X = hydrogen;
hydroxyl; or
hydroxyl group derivatized with an alkanoyl, aryloyl, alkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, or arylalkyloxycarbonyl group;

...with the proviso that...(4) when $R_1 = CR_{13}R_{14}R_{15}$, wherein $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, R_{15}, R_{14}, or R_{13}, respectively, cannot be...substituted or unsubstituted C_2-C_6-straight alkenyl...chain (emphasis added)" as set forth in claim 1 of the present application.

Since the above amendments to claim 1 exclude the possibility of R_{15}, R_{14}, or R_{13} being a substituted C_2-C_6-straight alkenyl chain, when $R_1 = CR_{13}R_{14}R_{15}$, where $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, the provisional rejection of claim 1 under the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-10 of Molino II is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: October 17, 2006

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Ruth R. Smith
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